

The Reporter

THE TECHNICAL NEWSLETTER FROM SUPELCO

Analysis of Antiretrovirals Used in Combination HIV Therapy

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Abstract

The simultaneous determination of antiretrovirals from three therapeutic classes is demonstrated using the Supelco Ascentis™ RP-Amide column.

Introduction

Antiretroviral agents are used in the treatment of human immunodeficiency virus (HIV) and acquired immuno deficiency syndrome (AIDS). To date, five therapeutic classes have been developed; nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), protease inhibitors (PIs) and fusion inhibitors (1). Effective treatment is usually accomplished using at least three drugs from more than one therapeutic class. For example, recommendations for initial treatment include the combination of two NRTIs or NtRTIs with either an NNRTI or a PI (2).

In the study of drug efficacy, pharmacokinetics, prevention and management of adverse reactions, therapeutic drug monitoring of antiretrovirals is performed. This is generally achieved by HPLC coupled with UV-diode array or mass spectrometry detection following solid phase extraction (3,4). Drawbacks of previous HPLC methods include the use of ion-pair reagents (5) and limited specificity for a single drug class (6). This report describes a simple HPLC method for the simultaneous determination of antiretrovirals from three drug classes using a new proprietary surface optimized embedded polar group (EPG) stationary phase, Ascentis RP-Amide. The Supelco Ascentis RP-Am-

ide phase demonstrates advantages in polar analyte retention as well as improved selectivity when compared to traditional C18 stationary phases.

Experimental Approach

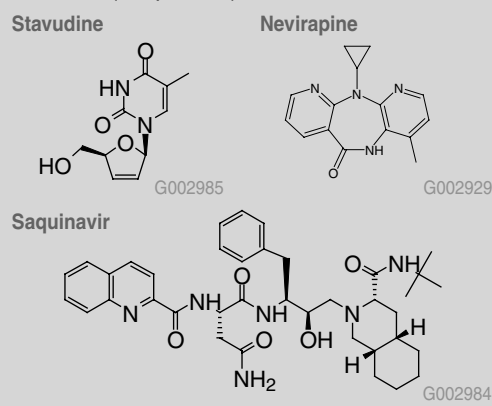
The USP assay method for nevirapine was modified by applying a gradient to include assay of other antiretrovirals. Alternately, if a MS detector is desired, minor adjustments to the mobile phase can be made. All chemicals utilized were obtained through Sigma-Aldrich and Riedel-de Haën. Analytes were obtained from USP or other sources.

Results

Representative structures from three drug classes and an optimized chromatogram obtained on the Ascentis RP-Amide EPG phase for the simultaneous analysis of seven antiretrovirals are provided in Figures 1 and 2A, respectively. When zalcitabine is added to the analyte mixture (Figure 2B), a small interfering peak appears as a shoulder on peak 8. The shoulder appears only after zalcitabine is analyzed

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Figure 1. Representative structures of an NRTI (Stavudine), an NNRTI (Nevirapine) and a PI (Saquinavir)



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Figure 2A. Separation of Seven Antiretrovirals Using the Supelco Ascentis RP-Amide

column: Supelco Ascentis RP-Amide, 15 cm x 4.6 mm I.D., 5 μ m particles (565324-U)
 mobile phase A: 25 mM ammonium phosphate (467782), pH 5.55 with phosphoric acid (345245)
 mobile phase B: acetonitrile (34851)
 flow rate: 1.0 mL/min.
 temp.: 35 $^{\circ}$ C
 det.: UV at 220 nm
 injection: 10 μ L
 sample: as indicated in 25 mM ammonium phosphate (pH 5.55)

Min.	%A	%B	
0	95	5	1. Lamivudine (50 μ g/mL)
10	15	85	2. Stavudine (50 μ g/mL)
12	15	85	3. Zidovudine (50 μ g/mL)
12.5	95	5	4. Nevirapine (35 μ g/mL)
			5. Saquinavir (100 μ g/mL)
			6. Ritonavir (100 μ g/mL)
			7. Lopinavir (100 μ g/mL)
			8. Zalcitabine (50 μ g/mL)

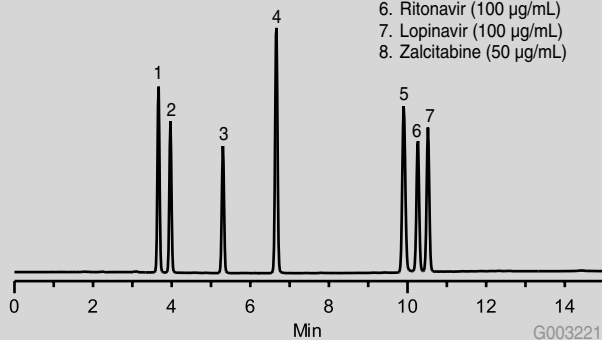
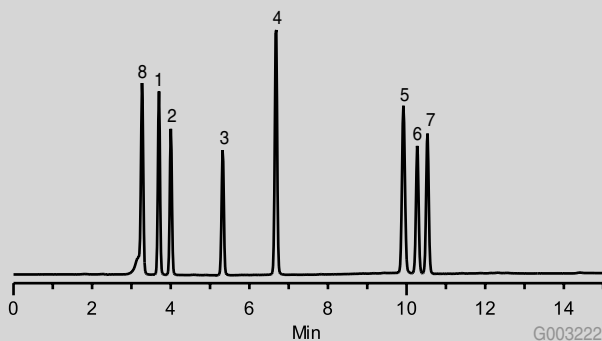


Figure 2B. Separation of Eight Antiretrovirals Using the Supelco Ascentis RP-Amide



(continued from page 1)

in combination with one or more of the protease inhibitors and thus appears to be a reaction product of the compounds.

For compatibility with mass spectrometric detection, the phosphate buffer initially employed was replaced with 0.1% ammonium acetate in water. Using this mobile phase in combination with acetonitrile, the elution of all 7 drugs was completed in 15 minutes (Figure 3).

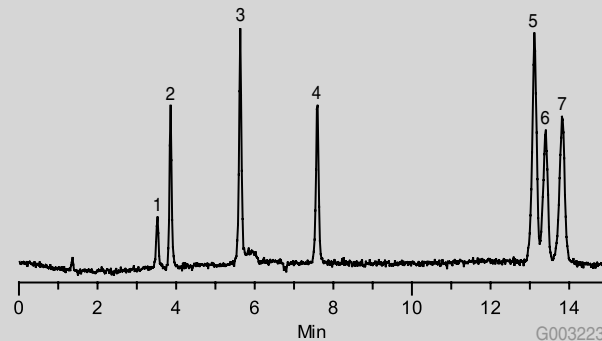
Conclusion

Simultaneous analysis of an NNRTI, nevirapine, NRTIs (lamivudine, zidovudine, stavudine), PIs (ritonavir, lopinavir, saquinavir) was achieved in a single run without the use of ion-pair reagents

Figure 3. Reconstructed Ion Chromatogram of Seven Antiretrovirals Using Supelco Ascentis RP-Amide and MS Detection

column: Supelco Ascentis RP-Amide, 15 cm x 4.6 mm I.D., 5 μ m particles (565324-U)
 mobile phase A: 0.1 % ammonium acetate (34674), pH 5.34 with acetic acid (33206)
 mobile phase B: acetonitrile (34851)
 flow rate: 1.0 mL/min.
 temp.: 35 $^{\circ}$ C
 det.: ESI (+), ESI (-)
 injection: 5 μ L
 sample: as indicated in 50:50, 0.1 % ammonium acetate (pH 5.34 with acetic acid): acetonitrile

Min.	%A	%B	
0	95	5	1. Lamivudine (3 μ g/mL)
10	40	60	2. Stavudine ESI (-), (12.5 μ g/mL)
15	40	60	3. Zidovudine ESI (-), (5 μ g/mL)
15.5	95	5	4. Nevirapine (1 μ g/mL)
			5. Ritonavir (2.5 μ g/mL)
			6. Saquinavir (2.5 μ g/mL)
			7. Lopinavir (2.5 μ g/mL)



utilizing a new EPG column. In comparison, alkyl type phases (C18 and C8) often require the use of ion pair reagents to achieve simultaneous monitoring of different therapeutic classes. Simultaneous monitoring of drugs used in combination therapy using the proprietary, surface optimized Ascentis RP-Amide stationary phase is advantageous in detecting interactions that can lead to clinical failures or shortfalls encountered in HIV treatment.

References

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Description	Cat. No.
Ascentis RP-Amide column, 15 cm x 4.6mm I.D., 5 μ m	565324-U
Ammonium phosphate	467782
Phosphoric acid	345245
Acetonitrile	34851
Ammonium acetate	34674
Acetic acid	33206

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Recovery & Sample Cleanup of Pesticides in Spinach Using Supelclean ENVI-Carb-II/PSA SPE

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Introduction

The multi-residue surveillance of pesticides in agricultural/food products is an ongoing project for regulatory agencies and industrial laboratories worldwide. Hundreds of thousands of samples are analyzed annually to meet a variety of purposes including regulatory enforcement and surveillance monitoring.

In the previous issue of *The Reporter* (Vol. 23.2), we discussed the utility of dual-layer ENVI-Carb™-II/PSA technology for the removal of matrix interferences when conducting GC-MS analysis of multi-residue pesticides. The article offered detailed description of the SPE chemistry and gave qualitative examples for the removal of pigments from spinach and the reduction of background interference in milk.

In this issue of *The Reporter*, we offer quantitative data by demonstrating the high recovery and sample cleanup of 18 pesticides from spinach using Supelclean™ ENVI-Carb-II/PSA SPE and Equity™-1 GC-MS.

Technology Description

Food samples are initially extracted/homogenized with a water miscible solvent (e.g. acetonitrile or acetone) in the presence of sodium chloride. The presence of sodium chloride drives phase separation between the solvent and endogenous aqueous residues within the sample. Upon centrifugation/filtration to remove particulate matter, the acetonitrile layer of the supernatant/filtrate is removed and dried over anhydrous sodium sulfate or magnesium sulfate. At this point, the acetonitrile extract is unsuitable for further analysis due to the high levels of endogenous interferences co-extracted with the pesticides during initial solvent extraction. SPE is necessary for further cleanup prior to GC-MS.

Figure 1. Supelclean ENVI-Carb-II/PSA SPE Tube



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Supelclean ENVI-Carb-II/PSA SPE is a dual-layer SPE cartridge (Figure 1). After the initial acetonitrile extract is concentrated, it is applied to a pre-conditioned ENVI-Carb-II/PSA SPE tube. The tube acts as a chemical filter in which pigments and sterols are retained on the ENVI-Carb-II layer (graphitized carbon), while fatty acids, organic acids, polar pigments, and sugars are trapped on the PSA (primary-secondary amine) layer. Pesticides are weakly retained on the tube and subsequently eluted with acetonitrile/toluene (3:1). Although the use of a vacuum manifold is recommended, the tubes are also amenable to gravity driven applications.

Experimental Approach

The performance of the SPE technology was evaluated by spiking spinach with a representative pesticide test mix. The mix represented a range of pesticide classes with varying physico-chemical properties. Included within this test mix were highly polar pesticides such as carbaryl, dichlorovos, acepate, and procymidone, which are primarily analyzed by LC.

Pesticides were spiked at the level of 0.2 ppm into 10 g fresh spinach. The mixture was carefully homogenized and extracted with acetonitrile/sodium chloride. The excess of acetonitrile was evaporated to ~1 mL under nitrogen at 40 °C, and the resulting extract was loaded onto the Supelclean ENVI-Carb-II/PSA SPE tube, 500 mg/300 mg/6 mL, preconditioned with 5 mL acetonitrile:toluene (3:1). Pesticide elution was facilitated with 20 mL acetonitrile:toluene (3:1). The SPE eluate was evaporated and reconstituted with 1 mL hexane:acetone (1:1) for subsequent GC-MS analysis.

To compensate for 'matrix effects', matrix match standards were prepared by spiking pesticides into blank spinach extracts subjected to the SPE process.

High Recoveries and Good Sample Cleanup

Recovery for the 18 pesticides tested averaged at 96%. Highly polar pesticides such as dichlorovos and methamidophos may be over-retained on the PSA sorbent due to secondary normal-phase (polar-polar) interactions resulting in poor recovery. At least 70% recovery was observed for all pesticides tested. In this application example with the exception of acepate (60% recovery). Table 1 lists recovery values for the pesticides tested.

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SPE

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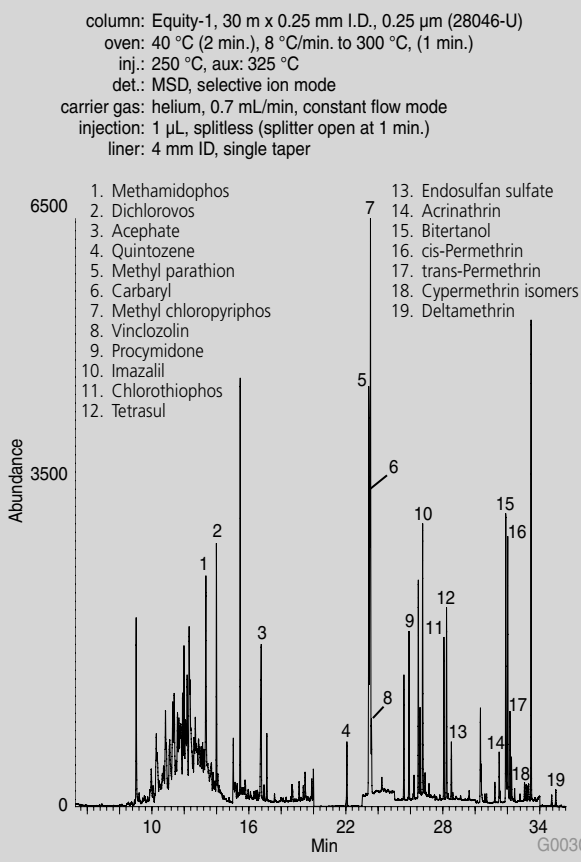
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Table 1. Recovery of Pesticides from Spinach Using Supelclean ENVI-Carb-II/PSA SPE

Peak ID	Compound	Pesticide Class	Pesticide Recovery (%)
1	Methamidophos	Organophosphorous	80
2	Dichlorovos	Organophosphorous	70
3	Acephate	Organophosphorous	60
4	Quintozene	Organochloride	92
5	Methyl parathion	Organophosphorous	97
6	Carbaryl	Carbamate	128
7	Methyl chloropyriphos	Organophosphorous	99
8	Vinclozolin	Organochloride	83
9	Procymidone	Dicarboximide	84
10	Imazalil	Imidazole	104
11	Chlorothiophos	Phosphosulfide	106
12	Tetrasul	Organochloride	87
13	Endosulfan sulfate	Organochloride	124
14	Acrinathrin	Organophosphorous	118
15	Bitertanol	Biphenol	108
16	Permethrin cis and trans	Pyriethroid	82
17	Cypermethrin isomers	Organochloride	74
18	Deltamethrin	Organobromine	134

Excellent sample cleanup was observed signified by sharp peaks and low background (Figure 2).

Figure 2. Representative Chromatogram of Pesticides Spiked into Spinach Followed by Supelclean ENVI-Carb-II/PSA SPE



Conclusion

Dual-layer SPE cartridges provide efficient sample cleanup of food samples, decreasing background interference levels during GC-MS analysis. Recoveries for most of the more challenging polar pesticides were 70% or greater. Table 2 describes the benefits of dual-layer SPE technology for pesticide analysis in food/agricultural products.

Table 2. Benefits of Supelclean ENVI-Carb-II/PSA SPE

- Decrease background levels for trace pesticide detection
- Reduce matrix-induced signal enhancement and suppression
- Relieve stress and reduce down time on the GC system
- Offers good recovery of pesticides including polar pesticides (e.g. methamidophos)

Supelclean SPE Tubes

Standard	Qty.	Cat. No.
Supelclean ENVI-Carb-II/PSA SPE Tube		
500 mg/500 mg/6 mL	30	54067-U
500 mg/300 mg/6 mL	30	55119-U
Supelclean ENVI-Carb-II/SAX/PSA SPE Tube		
500 mg/500 mg/500 mg/12 mL	20	52574-U
Supelclean SAX/PSA SPE Tube		
250 mg/250 mg/6 mL	30	52576-U
500 mg/500 mg/6 mL	30	52577-U
Supelclean PSA SPE Tube		
200 mg/3 mL	54	52578-U
500 mg/6 mL	30	52579-U
Supelclean ENVI-Carb SPE Tube		
100 mg/1 mL	108	57109-U
250 mg/3 mL	54	57088
250 mg/6 mL	30	57092
500 mg/6 mL	30	57094

For a complete listing of all Supelco SPE products for pesticide analyses, log on to our website: sigma-aldrich.com/spe-pesticide

! Related Information

For more technical information request *Extraction of Pesticides from Agricultural Products Using Multi-Layer ENVI-Carb-II/PSA SPE Tubes*, T405060 (HYA).

For a comprehensive list of standards, request our *Analytical Standards Catalog*, (GVQ).

For more information on Equity Capillary GC columns, request our *Equity brochure* (FAQ).

Optimizing Your Automated System for SPME

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With the development of new applications for SPME, the need for automation has greatly increased. The most commonly used autosampler is manufactured by CTC Analytics, and referred to by trade names such as CombiPAL™ or MPS-2. This instrument has the capability to handle samples in a variety of different modes.

Common SPME Automation Problems

One of the most common modes is headspace SPME with heat and agitation. When this mode is utilized, the vial is placed in a heating box that rotates in a circular motion. This rotating motion agitates the sample and improves recovery, thereby shortening extraction time. Even though the vial is rotating, the SPME holder remains in a fixed position while the needle is inserted into the vial. The rotating motion of the needle can cause it to bow or not remain straight. Subsequent stress on the needle such as penetration of septa may cause the needle to severely bend rendering it unusable. While this problem was slightly rectified by using stronger 23 gauge needles, it did not totally resolve the problem.

The square cut stainless steel needle used in the SPME fiber assemblies is not compatible with thick headspace vial septa. The needle has difficulty puncturing these thick septa. Even worse, if the needle is bowed from the agitation, the stress on the needle increases when trying to puncture the vial septa. Often, this process further damages the needle, eventually causing it to break. In addition, most vial caps used to seal the septa have small openings (5 mm). A bowed needle may not be properly centered on the narrow opening, hitting the metal cap, causing the needle to break.

Another commonly encountered problem is septa coring in the GC injection port. The square cut 23 GA needle can core septa. Fragments of the septa can then jam in the needle. When this happens, the thin plunger can bend when attempting to expose the fiber, or the fiber coating can be stripped off the core. In addition, septa particles in the inlet can bleed and also damage the fiber coating.

Solutions to these Problems

To resolve these compatibility and/or durability problems between SPME and autosamplers, several new products have been developed. These products include a new fiber assembly design, optimized SPME vials and septa, and the use of septum free GC inlet sealing systems.

New Assembly Design

A new fiber assembly has been designed by Supelco that is manufactured from a metal alloy containing shape memory properties. The metal fiber can be repeatedly flexed yet still retain its



Figure 1. New “Super-elastic” SPME Fiber Assembly

straight shape. The needle, plunger, and fiber core are manufactured out of this metal alloy with “super-elastic” properties (See Figure 1). The plunger is made of a thicker solid rod that is much stronger than previous rods and helps to reinforce the flexible piercing needle

with a tapered tip. The metal fiber is crimped into a hole drilled in the plunger. This eliminates the use of an epoxy to attach the fiber. This newly designed assembly is more durable and much less likely to break when using the autosampler.

The metal alloy is highly inert and does not contain iron. The use of the alloy as a fiber core appears to be as inert as fused silica. Figure 2 (pg. 6) compares the various SPME fiber cores with the extraction of a sample containing amines that are typically reactive with steel.

Headspace Vials Developed for SPME

Most headspace vials were developed to withstand high pressures commonly encountered by heating aqueous based materials above 100 °C. This is why most headspace vials have thick septa and caps with small openings. These thicker septa represent a greater challenge for the SPME fibers in trying to penetrate the septa without stressing the fiber assembly. However, with headspace SPME, typical sampling temperatures are below 70 °C. Thus, thinner vial septa (1.0 – 1.6 mm thick) can be used that are sealed with 8 mm opening caps. These thinner septa are much easier to penetrate by the SPME fiber assembly. The key was to develop vials that will seal tightly with thinner septa. This was accomplished by developing vials with screw cap necks with screw cap lids and SPME flat neck vials with tin crimped top lids. The lids typically contain PTFE lined silicone septa that are 1.5-1.6 mm thick. Research by Bruno Baltensperger at CTC Analytics compared the sealing capability of various vials. A summary of these results is shown in Figure 3 (pg. 6).

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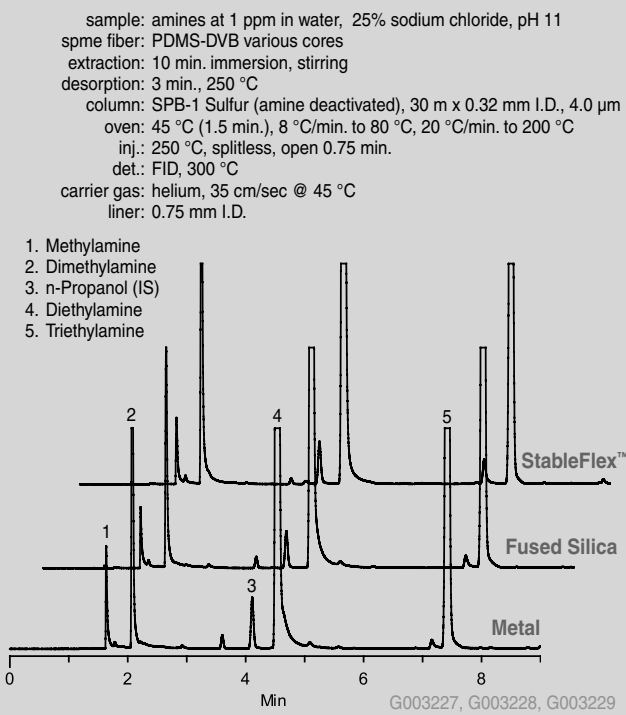
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SPME

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Figure 2. Comparison of Amine Response vs. Fiber Cores (PDMS-DVB)



(continued from page 5)

Using Septumless Sealing Inlets

The newly designed metal fiber assembly with the tapered tip does pierce vial septa more easily, but it can severely core inlet septa. This can cause potential problems as previously explained, so we highly recommend the use of inlet sealing devices that do not use silicone septa.

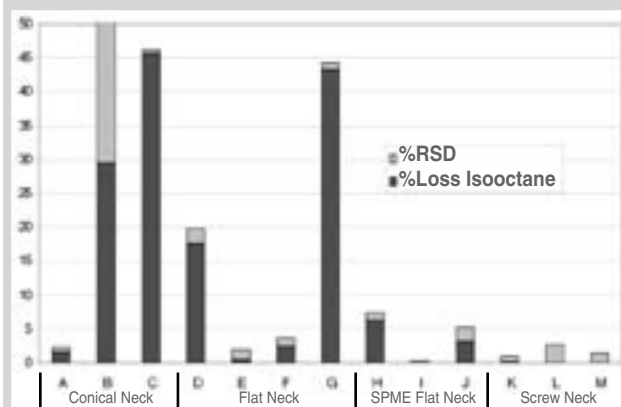
Our research has shown that Merlin Microseals™ are highly compatible with the new fiber assembly. Even with the tapered tip, the high pressure Microseals are durable and last a long time.

GERSTEL has demonstrated that the CIS-3/CIS-4 inlet is compatible with the new super-elastic fiber assembly. They have shown that the inlet can handle repeated extractions without damaging the inlet or fiber needle tip.

Conclusions

To get the best performance from SPME in your CTC Analytics autosampler, we highly recommend that you use a combination of products. The new super-elastic metal alloy assembly is more durable and will last longer than standard stainless steel assemblies. The life can be further improved by using vials and septa recommended for SPME use. Lastly, to minimize down time, changing of liners and improved chromatography, we recommend the use of septum free inlet sealing devices such as Merlin Microseals or GERSTEL CIS injectors.

Figure 3. Percent Loss of Isooctane and %RSD for Various Vials and Closures



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- A. Conical neck vials w/3 mm silicone PTFE septa and aluminum/tin closures with 8 mm hole
- B. Conical neck vials w/3 mm silicone PTFE septa and steel closures with 5 mm hole
- C. Conical neck vials w/3 mm butyl black septa and steel closures with 5 mm hole
- D. Flat neck vials w/3 mm silicone PTFE septa and steel closures with 5 mm hole
- E. Flat neck vials w/3 mm silicone PTFE septa and aluminum/tin closures with 8 mm hole
- F. Flat neck vials w/3 mm butyl black PTFE septa and steel closure with 5 mm hole
- G. Flat neck vials w/3 mm butyl black septa and steel closure with 5 mm hole
- H. SPME flat neck vials w/0.5 mm Viton™ septa and steel closure with 8 mm hole
- I. SPME flat neck vials w/1.0 mm Viton septa and steel closure with 8 mm hole
- J. SPME flat neck vials w/1.5 mm silicone PTFE septa and steel closure with 8 mm hole
- K. Screw neck vial w/1.5 mm silicone PTFE septa and steel closure with 8 mm hole
- L. Screw neck vial w/1.3 mm silicone PTFE septa and steel closure with 8 mm hole
- M. Screw neck vial w/1.5 mm butyl PTFE septa and steel closure with 8 mm hole

SPME Metal Fibers

Description	Cat. No.
100 µm PDMS	57928-U
30 µm PDMS	57922-U
7 µm PDMS	57919-U

Related Products

Description	Cat. No.
Vials for CTC Autosampler (100 µl)	
Screw cap vial, 10 mL, clear, 22.5 x 46 mm	SU860099
Screw cap vial, 10 mL, amber, 22.5 x 46 mm	SU860100
Screw cap vial, 20 mL, clear, 22.5 x 75.5 mm	SU860097
Screw cap vial, 20 mL, amber, 22.5 x 75.5 mm	SU860098
Screw cap, 18 mm, PTFE/silicone septa, thickness 1.3 mm	SU860101
Screw cap, 18 mm, PTFE/silicone septa, thickness 1.5 mm	SU860103
Crimp seal vial, 20 mL, clear	SU860104
Crimp cap, magnetic with Viton septa, thickness 1 mm	SU860106
Merlin Microseals	
Agilent/HP 5800, 5900, 6890 1 nut, 2 septa	24814-U
Agilent/HP 5800, 5900, 6890 1 nut, 1 septum	24815-U
Agilent/HP 5800, 5900, 6890 1 septum	24816-U
Varian 3400, 3600 1 nut, 1 septum, 1 inlet adapter & O-ring	24817-U
Varian 3400, 3600 1 septum	24818-U
Varian CP-1177 1 nut, 1 septum, 1 inlet adapter	22609-U

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SPME Inlet Liners

A regular schedule of inlet liner replacement will help prevent adsorption problems that can otherwise drastically affect your analysis.

Our liners feature:

- High temperature silanization to ensure inertness
- Consistent dimensions, tolerances, and quality
- In-house manufacturing that meets or exceeds instrument specifications of manufacturer



SPME Inlet Liners

Liner Type	Instrument Manufacturer	Dimension Length x OD x ID (mm)	Pkg. Size	Cat. No.
Direct	Agilent® 4890, 5880, 5890	78.5 x 6.5 x 0.75	1	2637501
			5	2637505
			25	2637525
Direct	Finnigan 9100 GCQ	78.5 x 6.5 x 0.75	1	2637501
			5	2637505
			25	2637525
SPME	PerkinElmer®	92 x 0.25 x 0.75	5	2631205
Splitless	Shimadzu, SPL-G9/15 Injector	127 x 5.0 x 0.75	1	2632901
			5	2632905
SPME/Splitless	Shimadzu®, SPL-14 Injector	99 x 5.0 x 0.75	1	2633501
			5	2633505
SPME/Splitless	Shimadzu, SPL-17 Injector	95 x 5.0 x 0.75	1	2633901
			5	2633905
			25	2633925
SPME	Thermo 8000 and TRACE	105 x 8.0 x 0.8	1	2876601-U
			5	2876605-U
SPME/Splitless	Varian® 1075/1077	74 x 6.35 x 0.75	1	2635801
			5	2635805
			25	2635825
Direct/SPME	Varian 1093/1094 SPI	54 x 4.6 x 0.8	1	2636401
			5	2636405
			25	2636425
Direct	Varian CP-1177	78.5 x 6.5 x 0.75	1	2637501
			5	2637505
			25	2637525

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Patent

SPME - Technology licensed exclusively to Supelco. US patent #5,691; European patent #523,092

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NEW! Acid Herbicide Standards

We are pleased to announce the addition of six new acid herbicide mixes to our chemical standards product line. They are appropriate for use in monitoring soil, drinking water, and ground-water for contamination, as well as acid herbicide residue on foods. All raw materials and solvents used in the preparation of Supelco brand mixes are screened for purity. Mixtures are gravimetrically prepared and then chromatographically assayed.

Each acid herbicide mix is supplied with a certificate of analysis. Data packets are also available, free of charge, upon request. Each data packet documents the rigorous analytical methods we use to verify raw material identity and purity, and provides certification as to the purity and final concentration accuracy.

Description	Composition	Cat. No.
Acid Herbicide Mix	1x1 mL, Methanol, Varied Conc. 2,4,5-T Dalapon MCPA 2,4,5-TP Dicamba MCPP 2,4-D Dichlorprop Pentachlorophenol 2,4-DB Dinoseb Picloram	861164
Acid Herbicide Spiking Mix	1x1 mL, Methanol, Varied Conc. 2,4,5-T Dalapon MCPA 2,4,5-TP Dicamba MCPP 2,4-D Dichlorprop Pentachlorophenol 2,4-DB Dinoseb	861386-U
Acid Herbicide Mix	1x1 mL, Methanol, Varied Conc. 2,4,5-T Dalapon Dinoseb 2,4-D Dicamba MCPA 2,4-DB Dichlorprop MCPP	861194
Herbicide Spiking Mix 1	1x10 mL, Acetone, Varied Conc. 2,4,5-T 2,4-Dichlorophenylacetic acid	861258
Acid Herbicide Spiking Mix 2	1x10 mL, Acetone, Varied Conc. 2,4,5-T 2,4,5-TP 2,4-D	861259
Acid Herbicide Spike Mix 3	1x10 mL, Acetone, 50 µg/mL 2,4,5-TP Dalapon 2,4-D Dinoseb	861263

Description	Concentration	Cat. No.
Methyl Herbicide Mix 1	1x1 mL, Hexane, Varied Conc. 2,4,5-T Methyl Ester Dichlorprop Methyl Ester 2,4-D Methyl Ester Dinoseb Methyl Ester 2,4-DB Methyl Ester MCPA Methyl Ester Dalapon Methyl Ester MCPP Methyl Ester Dicamba Methyl Ester Silvex® (2,4,5-TP) M.E.	861264

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